Docket No.: 22116-00005-US5
(PATENT)

#9
4/25/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Nicolaas M.J. Vermeulin, et al

Application No.: 09/713,512 Group Art Unit: 1621

Filed: November 14, 2000 Examiner: Peter G. O'Sullivan

For: POLYAMINE ANALOGUES AS THERAPEUTIC AND DIAGNOSTIC AGENTS

RESPONSE

Commissioner for Patents
Washington, DC 20231

Dear Sir:

This is in response to the Office Action mailed October 22, 2002.

Claims 36-61, 63-77 and 88-95 are now in the application.

The provisional rejection of claims 36-61, 63-77 and 88-95 under the judicially created dotrine of obviousness type double patenting as being unpatentable over the claims of copending application S.N. 09/396,523 will be overcome by the filing of a terminal disclaimer. Such will be filed upon overcoming the remaining rejections in the cases. The filing of a terminal disclaimer is not to be construed as an admission, estoppel or acquiescence. See *Quad Environmental Technology v. Union Sanitary District*, 20 USPQ2d 1392 (Fed. Cir. 1991) and *Ortho Pharmaceuticals Corp. v. Smith*, 22 USPQ2d 1119 (Fed. Cir. 1992).

The rejection of claims 36-41, 44-52, 60 and 61 under 35 USC 103(a) as being unpatentable over Cherksey is not deemed tenable. Cherksey does not render obvious claims 36-41, 44-52, 60 and 61 since, among other things, Cherksey does not disclose the claimed

stereoisomeric form of the claimed compounds, and does not lead one skilled in the art to select the claimed stereoisomers as possessing the beneficial results. As recognized by the Examiner, applicants have provided a showing of beneficial results for the claimed stereoisomers (see page 3, lines 3 and 4 of the Office Action). However, the rejection of claims 36-41, 44-52, 60 and 61 was maintained based upon the incorrect premise that "it is expected that there will be differences in activity of various stereoisomers in biological systems", and the reliance upon *In re Adamson*, 125 USPQ 233 and *In re May*, 197 USPQ 601.

Even if the above conclusory statement were accurate, which it is not, the claims are still patentable since the cited art does not suggest which of the stereoisomers would possess the better properties. The statement is merely an invitation to experiment. Accordingly, the rejection is in the nature of the impermissible standard of "ought to be tried". See *Jones v. Hardy*, 220 USPQ 1021 (Fed. Cir. 1984).

The degree of differential activity exhibited by stereoisomers of biological molecules is extremely variable and must be determined empirically. In fact, many enzymes will show marked stereospecificity for one class of inhibitors, while not distinguishing between enantiomers of another class. For example, the four stereoisomers of alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid, all bind and inhibit carboxypeptidase A with similar inhibition constants. Chung *et al.*, *J. Org. Chem.* 66:6462-71 (2001). However, the D-configuration of another carboxypeptidase A inhibitor, N-Hydroxyaminocarbonyl)phenylalanine, binds the enzyme three times tighter than the corresponding L-configuration. Chung and Kim, *Bioorg. Med. Chem.* 9: 185-9 (2001). Generally, it has been suggested that inhibitors of an enzyme's ground state may show marked stereospecificity, where irreversible and mechanism based inhibitors may show little or no stereospecificity. Kim, D.H., *Mini Rev. Med. Chem.* 1:155-61 (2001). Accordingly, the potential degree of stereospecificity that may be demonstrated by the claimed compounds cannot be predicted.

The cases relied upon by the Examiner do not suggest otherwise. For instance, *In re May* found the claims rejected under 35 USC 103 to be patentable. Only the claims that were anticipated stood the test of unpatentability under 35 USC 102.

The earlier case relied upon, *In re Adamson*, involved a rejection based on a combination of at least two references. If anything it is at odds with *In re May*, as well as with *In re Williams*,

80 USPQ 150 which was cited with approval in *In re May*. In *Williams*, the Court stated that the novelty of an optical isomer is not negated by prior art disclosure of the racemate.

Furthermore, *In re Adamson* differs from the present situation. In particular, the facts of Adamson involved differences in the same activity between the L- and O- forms of a compound. In the present case, differences in a different activity (tissue accumulation) as well as an additional activity (polyamine transport inhibition) have been shown.

Also, the rejection fails to take into account more recent case law concerning 35 USC 103 as enunciated by the Federal Circuit.

Also see *In re Nathan*, 140 USPQ 601 (CCPA 1964) and *In re Magerlein*, 145 USQP 683 (CCPA 1965) which, although involving a different issue, illustrate the patentability of claims directed to specific stereoisomers of a prior art compound.

The rejection is also inconsistent with the plethora of issued patents directed to specific stereoisomers of prior art compounds. See, for instance, U.S.P. 4,871,852 (copy attached).

Also, the mere fact that cited art may be modified in the manner suggested by the Examiner does not make this modification obvious, unless the cited art suggest the desirability of the modification. No such suggestion appears in the cited art in this matter. The Examiner's attention in kindly directed to *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), *In re Dembiczak et al.* 50 USPQ2d. 1614 (Fed. Cir. 1999), *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984), *In re Laskowski*, 10 USPQ2d. 1397 (Fed. Cir. 1989) and *In re Fritch*, 23, USPQ2d. 1780 (Fed. Cir. 1992).

In Dembiczak et al., supra, the Court at 1617 stated: "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., C.R. Bard, Inc., v. M3 Sys., Inc., 157 F.3d. 1340, 1352, 48 USPQ2d. 1225, 1232 (Fed. Cir. 1998) (describing 'teaching or suggestion motivation [to combine]' as in 'essential evidentiary component of an obviousness holding'), In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d. 1453, 1459 (Fed. Cir. 1998) ('the Board must identify specifically...the reasons one of ordinary skill in the art would have been motivated to select the references and combine them');...".

Also, the cited art lacks the necessary direction or incentive to those or ordinary skill in the art to render a rejection under 35 USC 103 sustainable. The cited art fails to provide the

degree of predictability of success of achieving the properties attainable by the present invention needed to sustain a rejection under 35 USC 103. See *Diversitech Corp. v. Century Steps, Inc.* 7 USPQ2d 1315 (Fed. Cir. 1988), *In re Mercier*, 185 USPQ 774 (CCPA 1975) and *In re Naylor*, 152 USPQ 106 (CCPA 1966).

Moreover, the properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 USC 103. See *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d. 1923 (Fed. Cir. 1990), *In re Antonie*, 195, USPQ 6 (CCPA 1977), *In re Estes*, 164 USPQ (CCPA 1970), and *In re Papesch*, 137 USPQ 43 (CCPA 1963).

No property can be ignored in determining patentability and comparing the claimed invention to the cited art. Along these lines, see *In re Papesch*, supra, *In re Burt et al*, 148 USPQ 548 (CCPA 1966), *In re Ward*, 141 USPQ 227 (CCPA 1964), and *In re Cescon*, 177 USPQ 264 (CCPA 1973).

In view of the above, consideration and allowance are, therefore, respectfully solicited.

In the event that the Examiner believes an interview might serve to advance the prosecution of this application in any way, the undersigned attorney is available at the telephone number noted below.

The Commissioner is hereby authorized to charge any fees or credit any overpayment associated with this communication including any extension fees to Deposit Account No. 22-0185.

Dated: February 24, 2003

Respectfully submitted,

By _____

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1: J Med Chem 2002 Feb 14;45(4):911-8 Related Articles, Links

Cysteine derivatives as inhibitors for carboxypeptidase A: synthesis and structure-activity relationships.

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A series of cysteine (Cys) derivatives having an alkyl or arylalkyl moiety on the alpha-amino group of the amino acid have been synthesized as a novel type of inhibitor for carboxypeptidase A. These compounds are readily prepared starting with Cys in an optically active form. The structure-activity relationship study revealed that the inhibitors prepared from D-Cys are much more potent than the corresponding inhibitors obtained from L-Cys, and the most potent inhibitor in the series, (S)-1j with a K(i) value of 55 +/- 4 nM, is obtained by introducing a phenethyl moiety on the amino group of D-Cys. In comparison, the most active inhibitor in the series of 2-substituted 3-mercaptopropanoic acid is found to be 20, in which the phenyl ring is linked to the mercaptocarboxylic acid at the alpha-position with a methylene unit. A proposal that accounts for the different structural requirement for the maximum activity between the two series of inhibitors is provided.

PMID: 11831903 [PubMed - indexed for MEDLINE]

1: Bioorg Med Chem 2001 Jan;9(1):185-9

Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

N-(Hydroxyaminocarbonyl)phenylalanine: a novel class of inhibitor for carboxypeptidase A.

Chung SJ, Kim DH.

Center for Biofunctional Molecules and Department of Chemistry, Pohang University of Science and Technology, Namgu, South Korea.

N-(Hydroxyaminocarbonyl)phenylalanine (1) was designed rationally as a new type of inhibitor for carboxypeptidase A (CPA). The designed inhibitor was readily prepared from phenylalnine benzyl ester in two steps and evaluated to find that rac-1 inhibits CPA in a competitive fashion with the Ki value of 2.09 microM. Surprisingly, inhibitor 1 having the D-configuration is more potent (Ki = 1.54 microM) than its antipode by about 3-fold. A possible explanation for the stereochemistry observed in the inhibition of CPA with 1 is presented.

PMID: 11197339 [PubMed - indexed for MEDLINE]

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1: Mini Rev Med Chem 2001 Jul;1(2):155-61 Related Articles, Links

Origin of chiral pharmacology: stereochemistry in metalloprotease inhibition.

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The stereospecificity shown by a wide variety of inhibitors that are effective for carboxypeptidase A (CPA), a representative zinc protease is analyzed on the basis of inhibitor type. In cases of ground state analog inhibitors and transition state analog inhibitors, the stereoisomers having the stereochemistry that corresponds to stereochemistry of substrate are more potent, but in the case of irreversible inhibitors including mechanism-based inactivators the preferred inhibitory stereochemistry cannot be predicted simply from the substrate stereospecificity. The Ogston's three point fit concept may be of great value in understanding the inhibitory stereochemistry of reversible competitive inhibitors. On the other hand, the stereochemistry of irreversible inhibitors may possibly be predicted on the ground of the transition state structure that plays a critical role in the inactivation pathway.

Publication Types:
- Review
- Review, Tutorial

PMID: 12369980 [PubMed - indexed for MEDLINE]

1: J Org Chem 2001 Sep 21;66(19):6462-71 Related Articles, Links

Mechanistic insight into the inactivation of carboxypeptidase A by alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid, a novel type of irreversible inhibitor for carboxypeptidase A with no stereospecificity.

Chung SJ, Chung S, Lee HS, Kim EJ, Oh KS, Choi HS, Kim KS, Kim YJ, Hahn JH, Kim DH.

Center for Biofunctional Molecules and Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, Korea.

On the basis of the active site topology and enzymic catalytic mechanism of carboxypeptidase A (CPA), a prototypical zinc-containing proteolytic enzyme, alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid (1), was designed as a novel type of mechanism-based inactivator of the enzyme. All four possible stereoisomers of the inhibitor were synthesized in an enantiomerically pure form starting with optically active aspartic acid, and their CPA inhibitory activities were evaluated to find that surprisingly all of the four stereoisomers inhibit CPA in a time dependent manner. The inhibited enzyme did not regain its enzymic activity upon dialysis. The inactivations were prevented by 2-benzylsuccinic acid, a competitive inhibitor that is known to bind the active site of the enzyme. These kinetic results strongly support that the inactivators attach covalently to the enzyme at the active site. The analysis of ESI mass spectral data of the inactivated CPA ascertained the conclusion from the kinetic results. The values of second-order inhibitory rate constants (k(obs)/[I](o)) fall in the range of 1.7-3.6 M(-1) min(-1). The lack of stereospecificity shown in the inactivation led us to propose that the ring cleavage occurs by the nucleophilic attack at the 2-position rather than at the 5-position and the ring opening takes place in an addition-elimination mechanism. The tetrahedral transition state that would be generated in this pathway is thought to be stabilized by the active site zinc ion, which was supported by the PM3 semiemprical calculations. In addition, alpha-benzyl-2-oxo-1,3-oxazolidine-5-acetic acid (18), a structural isomer of 1 was also found to inactivate CPA in an irreversible manner, reinforcing the nucleophilic addition-elimination mechanism. The present study demonstrates that the transition state for the inactivation pathway

plays a critical role in determining stereochemistry of the inactivation.

PMID: 11559199 [PubMed - indexed for MEDLINE]
